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PATENT

THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant : Charles E. Clum et al.

Serial No.: 700,165 Group No.: 125

Filed : February 11, 1985 Examiner : J. Lipovsky

For : SKIN CARE COMPOSITIONS

DECLARATION UNDER RULE 132

Honorable Commissioner of Patents and Trademarks
Washington, D. C. 20231

Dear Sir:

I, JAMES J. LEYDEN, declare and say:

THAT I received a B.S. Degree from St. Joseph's College in 1962 and an M.D. Degree from the University of Pennsylvania School of Medicine in 1966 and served a residency in Dermatology at the University of Pennsylvania and as Chief of Dermatology USAH at Ft. Devens;

THAT I have been affiliated with the faculty of the University of Pennsylvania School of Medicine since 1972 and have been a full Professor of Dermatology since 1983;

THAT I am a member of the Society of Investigative Dermatology, American Academy of Dermatology, Philadelphia Dermatologic Society, Philadelphia College of Physicians, American Society of Microbiology and the Society of Pediatric Dermatology and have served and currently serve on a number of medical and academic committees;

THAT I serve as a consultant to the U.S. Food & Drug Administration and the U.S. Federal Trade Commission, Health Protection Branch - Canada and the drug regulatory agencies of England, Germany and Austria;

THAT since January 1, 1985 I have served as a lecturer or visiting professor at the combined U.S. Army and U.S. Air Force Residency programs - Branch Army Hospital, Tulane University, University of Michigan, New York University, Yale University, Duke University and Columbia University;

THAT I have authored or co-authored over 160 articles concerning basic research, clinical research and/or case reports relating to various dermatological matters and further that I have authored or co-authored 33 books, chapters or reviews relating to dermatological matters;

THAT I have received various awards including in 1985 the Gold Award for Original Investigation by the American Academy of Dermatology;

THAT I am affiliated with Ivy Research Laboratories, Inc. which is an independent laboratory dealing with investigational studies of the safety and efficacy of a wide range of active ingredients and products in the field of dermatology. We also conduct basic investigational studies in skin science including the development of test procedures and models to facilitate the testing of skin products as well as the active ingredients therein.

THAT I have conducted tests and evaluations of thousands of skin care products over a period of fifteen years on both animal and human subjects and evaluated the efficacy and effects of said products;

THAT in 1982 I conducted studies for Johnson & Johnson Baby Products Company to determine the ability of various diaper rash formulations to inhibit the growth of Candida albicans on human skin;

THAT the test procedure was as follows: Ten subjects (four females and six males) with an age range of 19 to 27 years were randomized into a controlled double-blind study to compare the ability of four treatments to prophylactically inhibit the growth of Candida albicans on the arms of the subjects. Six test sites on the forearms of each subject were randomized according to the following treatment plan:

- a) Base (no actives)
- b) 15% zinc oxide in base
- c) 0.25 miconazole nitrate in base
- d) 0.25 miconazole nitrate and 15% zinc oxide
(1:60 ratio) in base
- e) no treatment

Twenty microliters of a saline suspension of Candida albicans containing 1 million cells per milliliter are applied to three one square centimeter test sites on the volar forearm surface of each volunteer subject. The areas are covered with an impermeable plastic film and secured with tape. The test sites are uncovered six hours after inoculation and treated with one of the test products or left untreated as a control. The sites are then redressed with plastic film for an additional 24 hours. The test products are then removed from all sites and cultures are obtained by the standard detergent scrub method of Williamson and Kligman. This method is set forth in the Journal of Investigative Dermatology, Vol. 45, No. 6, pps. 498-503 (1965).

THAT two different types of measurements and data were obtained from these tests; microbiological measurements and clinical measurements;

THAT the microbiological data was obtained as follows: cultures from all test sites collected as above were prepared on Trypticase Soy Agar and Littman Media plates and incubated for 48 hours. Colonies were then counted by standard microbiological methods.

THAT for each of the counts, miconazole alone gave lower counts than zinc oxide alone, but these difference were not statistically significant. For aerobes on Trypticase media, miconazole alone and zinc oxide alone each gave lower counts than the untreated site and the base. For Candida albicans on Trypticase media, miconazole alone gave lower counts than the base, while the remaining products do not differ. For Candida albicans on Littman media, counts with miconazole alone and zinc oxide alone were lower than the base, (but not different from each other or the untreated site. Results for the miconazole nitrate and zinc oxide product were significantly lower than all the other tested products. To determine if the relation between zinc oxide and miconazole was additive or synergistic, a second analysis of variance was performed without the untreated site. The model included zinc oxide, miconazole and the interaction of these ingredients. The results show a small but statistically significant synergistic effect.

THAT the clinical data was obtained as follows: measurements are obtained for each site immediately prior to treatment, at 24 hours and at 48 hours after treatment. Grading is done on a scale of 0=no reaction, 1=minute pinpoint papules and/or faint erythema, 2=at least 5 discrete papules or pustules and definite erythema, 3=greater than 10 papules or pustules and erythema, 4=confluent papules or pustules and intense erythema.

THAT the following clinical results were obtained: at 24 hours, reactions at the sites treated with base only were more severe than the other treatments, while the other products did not differ significantly. By 48 hours, the clinical severity had increased with all treatments except the zinc oxide-miconazole product. The zinc oxide-miconazole severity was directionally less than miconazole alone, and significantly less than all other treatments both by chi square tests and two-way analysis of variance.

THAT one could conclude from these tests that the clinical scores 48 hours after inoculation demonstrated that the combination of miconazole nitrate and zinc oxide was superior to miconazole alone and superior to the other treatments. Furthermore, the combination produced significantly lower counts of Candida albicans than all other treatments.

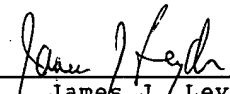
THAT in my opinion, these results demonstrate that both clinically and microbiologically the combination of 0.25% miconazole nitrate in a base containing 15% zinc oxide is superior to miconazole alone and the base and further that these results indicate a synergistic effect.

THAT the above test procedures are well recognized in the dermatological field and have been published, see for example, Journal of Investigative Dermatology, 72:165-170 (1979). A copy of said article is attached hereto.

THAT in my opinion, the above described test procedures and results therefrom clearly establish the efficacy and synergistic nature of miconazole nitrate - zinc oxide combinations in a 1:60 ratio against Candida albicans.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Subscribed this day of March 7 1986.



James J. Leyden

Post Office Address: .

